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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/536,804	11/10/2005	Magali Williamson	BJS-620-373	4496
23117	7590	01/22/2010	EXAMINER	
NIXON & VANDERHYE, PC 901 NORTH GLEBE ROAD, 11TH FLOOR ARLINGTON, VA 22203				REDDIG, PETER J
ART UNIT		PAPER NUMBER		
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Advisory Action Before the Filing of an Appeal Brief	Application No.	Applicant(s)
	10/536,804	WILLIAMSON ET AL.
	Examiner	Art Unit
	PETER J. REDDIG	1642

--The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

THE REPLY FILED 21 December 2009 FAILS TO PLACE THIS APPLICATION IN CONDITION FOR ALLOWANCE.

1. The reply was filed after a final rejection, but prior to or on the same day as filing a Notice of Appeal. To avoid abandonment of this application, applicant must timely file one of the following replies: (1) an amendment, affidavit, or other evidence, which places the application in condition for allowance; (2) a Notice of Appeal (with appeal fee) in compliance with 37 CFR 41.31; or (3) a Request for Continued Examination (RCE) in compliance with 37 CFR 1.114. The reply must be filed within one of the following time periods:

- a) The period for reply expires 3 months from the mailing date of the final rejection.
- b) The period for reply expires on: (1) the mailing date of this Advisory Action, or (2) the date set forth in the final rejection, whichever is later. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of the final rejection.

Examiner Note: If box 1 is checked, check either box (a) or (b). ONLY CHECK BOX (b) WHEN THE FIRST REPLY WAS FILED WITHIN TWO MONTHS OF THE FINAL REJECTION. See MPEP 706.07(f).

Extensions of time may be obtained under 37 CFR 1.136(a). The date on which the petition under 37 CFR 1.136(a) and the appropriate extension fee have been filed is the date for purposes of determining the period of extension and the corresponding amount of the fee. The appropriate extension fee under 37 CFR 1.17(a) is calculated from: (1) the expiration date of the shortened statutory period for reply originally set in the final Office action; or (2) as set forth in (b) above, if checked. Any reply received by the Office later than three months after the mailing date of the final rejection, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

NOTICE OF APPEAL

2. The Notice of Appeal was filed on _____. A brief in compliance with 37 CFR 41.37 must be filed within two months of the date of filing the Notice of Appeal (37 CFR 41.37(a)), or any extension thereof (37 CFR 41.37(e)), to avoid dismissal of the appeal. Since a Notice of Appeal has been filed, any reply must be filed within the time period set forth in 37 CFR 41.37(a).

AMENDMENTS

3. The proposed amendment(s) filed after a final rejection, but prior to the date of filing a brief, will not be entered because

- (a) They raise new issues that would require further consideration and/or search (see NOTE below);
- (b) They raise the issue of new matter (see NOTE below);
- (c) They are not deemed to place the application in better form for appeal by materially reducing or simplifying the issues for appeal; and/or
- (d) They present additional claims without canceling a corresponding number of finally rejected claims.

NOTE: _____. (See 37 CFR 1.116 and 41.33(a)).

4. The amendments are not in compliance with 37 CFR 1.121. See attached Notice of Non-Compliant Amendment (PTOL-324).

5. Applicant's reply has overcome the following rejection(s): _____.

6. Newly proposed or amended claim(s) _____ would be allowable if submitted in a separate, timely filed amendment canceling the non-allowable claim(s).

7. For purposes of appeal, the proposed amendment(s): a) will not be entered, or b) will be entered and an explanation of how the new or amended claims would be rejected is provided below or appended.

The status of the claim(s) is (or will be) as follows:

Claim(s) allowed: _____.

Claim(s) objected to: _____.

Claim(s) rejected: 106, 109 and 111.

Claim(s) withdrawn from consideration: 76-105 and 112-114.

AFFIDAVIT OR OTHER EVIDENCE

8. The affidavit or other evidence filed after a final action, but before or on the date of filing a Notice of Appeal will not be entered because applicant failed to provide a showing of good and sufficient reasons why the affidavit or other evidence is necessary and was not earlier presented. See 37 CFR 1.116(e).

9. The affidavit or other evidence filed after the date of filing a Notice of Appeal, but prior to the date of filing a brief, will not be entered because the affidavit or other evidence failed to overcome all rejections under appeal and/or appellant fails to provide a showing a good and sufficient reasons why it is necessary and was not earlier presented. See 37 CFR 41.33(d)(1).

10. The affidavit or other evidence is entered. An explanation of the status of the claims after entry is below or attached.

REQUEST FOR RECONSIDERATION/OTHER

11. The request for reconsideration has been considered but does NOT place the application in condition for allowance because:
See Continuation Sheet.

12. Note the attached Information Disclosure Statement(s). (PTO/SB/08) Paper No(s). _____

13. Other: _____.

/Peter J Reddig/
Examiner, Art Unit 1642

Continuation of 11. does NOT place the application in condition for allowance because: The amendment claims a new plexinB1 mutation, T5059C, which was not previously claimed, thus the amended claims would require further search and/or consideration and thus the proposed amendment will not be entered.

Claims 106, 109 and 111 remain rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement for the reasons set forth in section 4, pages 2-10 of the Office Action of September 25, 2009.

Applicants argue that they have demonstrated in the specification the existence of the recited mutations in prostate and breast cancers. Moreover, the specification describes, for example, on pages 22 and 29 of the substitute specification filed July 11, 2008 that the disclosed mutations in plexinB1 nucleic acid and polypeptide sequences are associated with invasive cancers which are prone to metastasis. Further, the specification describes the following on page 31 : "A decrease in activity [of the plexinB1 sequences containing the mutations of the invention] in the presence relative to the absence of test compound is indicative that the compound is a putative anti-cancer agent." Further, the Wong et al reference of record ("Plexin-B1 mutations in prostate cancer" PNAS, November 27, 2007, vol. 104, No. 48, 19040-9045) demonstrates that expression of mutant versions of the PlexinB1 gene increase the invasive capacity of the cells relative to wild type and vector controls (see page 19042, right column, last sentence of section titles Mutation of Plexin-B1 Increases Cell Motility and Invasion). Wong et al further confirm that the tested mutants have lost or have considerably reduced their ability to bind R-Ras and inactivate it.

"Cells expressing mutant Plexin-B1 will therefore have an increased ratio of active/inactive R-Ras relative to cells expressing WT Plexin-B1. Activated R-Ras activates integrins resulting in an increase in cell adhesion and motility. The finding of a loss of R-RasGAP activity for mutant Plexin-B1 is therefore consistent with our in vitro assays." See page 19044, left column, first full paragraph of Wong et al.

Applicants argue that Wong et al. conclude that

"Overexpression of Plexin-B1 protein in primary prostate cancers was also seen. Together these results suggest that Plexin-B1 has a role in prostate cancer progression." See page 19044, left column, second full paragraph of Wong et al.

Applicants argue that it is "clear" that expression of the Plexin-B1 sequence containing the A5653G mutation results in or is related to cancer progression and that identification of an agent which reduced expression of same according to the claims would be useful as a subject of further study as a putative anti-cancer agent, as claimed. One of ordinary skill in the art will be able to make and use the claimed invention without undue experimentation.

Applicants' arguments have been carefully considered, but have not been found persuasive because the amendment has not been entered and will not be entered for the reasons set forth above, therefore the claims have not been amended and remain drawn to numerous mutations of Plexin B-1 that have not been tested by Wong et al. for any activity toward cancer cells or otherwise. Thus the teachings of Wong et al. are not commensurate in scope with that of the claimed method and the rejection is maintained for the reasons previously set forth. Additionally, with regard to expression of the Plexin-B1 sequence containing the A5653G mutation Wong et al. has not shown that any changes in the expression of the nucleic acid comprising it affect the function or phenotype of any cancer cell and all of the functional assays were performed in HEK293 and COS-7 cells that are not cancer cells (see Figs. 3-6), thus the relevance of these effects to cancer cannot be predictably extrapolated. Furthermore, the statement on p. 31 of the specification appears to merely suggest an embodiment of the invention and does not show that any changes in the expression of anucleic acid comprising the A5653G mutation, or any other mutation, is indicative of anti-cancer activity.

Applicants argue that the claims do not require or relate to determining an increase in the wild-type Plexin-B1 to identify a putative anti-cancer agent. Clarification of the Examiner's criticisms in this regard is requested in the event the rejection is maintained based on same.

Applicants arguments have been considered and with regard to the claims not determining the wild type Plexin B1 expression have been found persuasive.

Applicants argue that the specification describes the claimed method of identifying a compound as a putative anti-prostate cancer or anti-breast cancer agent based on plexin-B1 sequences having specifically identified mutations. The finding of overlap in mutations found in breast and prostate cancers (i.e., positions 5059, 5069, 5458, 5452 and 5713) would reasonably suggest to one of ordinary skill in the art that testing of putative anti-cancer agents according to the claimed methods would identify anti-cancer agents useful in treating breast and prostate cancers. See Tables 1 and 2 of the specification and page 3 of the Office Action dated September 25, 2009. The Examiner's general reference to a 1985 textbook (i.e., Taber's Cyclopedic Medical Dictionary4) is not believed to be sufficient to demonstrate the alleged unpredictability of the presently claimed invention and/or the level of ordinary skill in the art at the time of the present application (i.e., 2003). The applicants again note that the claims relate to identification of putative anti- cancer agents for prostate and breast cancer. The Examiner's comments on page 3 of the Office Action dated September 25, 2009 relating to a variety of cancers are believed to be moot in view of the above.

Applicants' arguments have been carefully considered, but have not been found persuasive because the amendment has not been entered and will not be entered for the reasons set forth above, therefore the claims have not been amended and remain drawn to identifying a compound as an anti-cancer agent, not solely an anti-prostate or anti-breast cancer agent. Additionally, the description of the heterogeneity of cancer phenotypes was not solely based on the Taber citation and the heterogeneity of cancer phenotypes and etiologies is well known in the art as previously set forth. Thus, given that the specification has not shown that that any changes in the expression of the nucleic

acid comprising mutations in plexinB1 are indicative anti-cancer activity of an agent, the rejections remain for the reasons previously set forth given the claims remain broadly drawn to identifying a putative anti-cancer agent.

Applicants argue that similarly, the Examiner's criticisms on page 4 of the Office Action dated September 25, 2009 of the recitation of the range of mutants recited in the unamended claims are believed to be moot in view of the above.

Applicants' arguments have been carefully considered, but have not been found persuasive because the amendment has not been entered and will not be entered for the reasons set forth above, therefore the claims have not been amended to reduce the range of mutations claimed, thus the rejections remain for the reasons previously set forth

Applicants argue that as for the Examiner's dismissal of the results present in Wong et al. as being based on in vitro studies on cell lines "which do not predictably extrapolate to in vivo anti-cancer activity", the Examiner is requested to see, for example, the indication in Wong et al. that standard in vitro methods of identifying oncogenes "have not been feasible because of an inability to maintain exogenous expression of Plexin-B1 over time and will require inducible vectors." Wong et al. conclude however that "Plexin-B1 is likely to be a key player in cancer invasion and metastasis and is a potential target for anticancer therapy." One of ordinary skill in the art will believe that the results of Wong et al. may be predictably extrapolated to identify compounds as putative anti-prostate cancer or anti-breast cancer agents, as claimed.

Applicants argue that they further submit that the totality of the evidence in the specification and the art of record will be persuasive to one of skill in the art that the claimed plexin B1 mutations drive the development of and/or progression of cancer and that changes in the expression of mutant plexin B1 will affect cancer growth and progression.

Applicants argue that the specification discloses mutations in plexin B1 which occur at high frequency in prostate and breast cancer. This is confirmed by Wong et al (of record). Mutations found in cancer cells are discussed in Stratton MR et al, Nature 458: 719-724, 2009 (copy attached). In particular, Stratton et al describes the difference between passenger mutations, which are incidental mutations which are not related to cancer, and driver mutations, which provide a selective advantage to the cancer cells over normal cells and drive the development of and/or progression of cancer (see page 721 Box 1).

Applicants argue that it is clear from Stratton et al that many point mutations which are found in cancer cells are passenger mutations. However, the data provided by the specification, which is supported by Wong et al, provides convincing evidence that all the mutations of the claims are not passenger mutations, but are in fact driver mutations that are causative of carcinogenesis or drive the progression of the disease,

Applicants argue that the evidence that the claimed mutations are driver mutations can be summarised as follows,

1. The claimed mutations alter the amino acid sequence of the protein
2. The claimed mutations were independently confirmed using 2 methods
3. Many of the mutations were found in more than one cancer
4. The claimed mutations are somatic
5. The mutations were in a restricted region of the gene, The incidence of mutations in this region is 331 mutations/Mb DNA analyzed compared to 1,2 non functional mutations/Mb in the cancer genome as a whole.
6. The ratio of amino acid altering mutations to non-amino acid altering mutations (non-synonymous: synonymous ratio) was 73:1, compared to the 1:2 which would be expected for chance passenger mutations
7. Five of the claimed mutations are in evolutionarily highly conserved regions
8. Plexin B1 is known to interact with many known cancer genes (e.g. ErbB2, c-Met).
9. All four mutations tested altered the in vitro function of the plexin B1 protein.

Applicants' argue that the totality of all of the evidence summarized above would convince a skilled person that the claimed mutations in plexin B1 drive the development and/or progression of cancer and therefore altered expression of mutant plexin B1 will alter cancer growth and development.

Applicants argue that as for the predictability of extrapolating results from Wong et al. Stratton et al states at page 722 col 1; "Because cancer cells are dependent on the abnormal proteins encoded by mutated cancer genes, they have become targets for the development of new cancer therapeutics"

Applicants argue that in other words, one of ordinary skill in the art would reasonably expect that mutated cancer genes and their products would be targets for anti-cancer drugs. This is confirmed on page 722 cols 1-2, which state; "Because many [point-mutated cancer genes] are kinases that are activated by the mutations found in cancer, they have prompted a wave of drug discovery to find inhibitors that may serve as anticancer therapeutics, some of which are already in clinical trial".

Applicants argue that point-mutated cancer genes are therefore well-known in the art to provide potential targets for new drugs for cancer treatment and the mutated plexin B1 sequences which are described in the specification would be reasonably expected to be potential targets for anticancer drugs.

Applicants' arguments have been carefully considered, but have not been found persuasive because the amendment has not been entered and will not be entered for the reasons set forth above, therefore the claims have not been amended and remain drawn to numerous mutations of Plexin B1 that have not been tested by Wong et al. for any activity toward cancer cells or otherwise. Thus the teachings of

Wong et al. are not commensurate in scope with that of the claimed method and the rejection is maintained for the reasons previously set forth. Additionally, with regard to expression of the Plexin-B1 sequence containing the A5653G mutation or any other mutation Wong et al. has not shown that any changes in the expression of the nucleic acid comprising it affect the function or phenotype of any cancer cell and all of their functional assays were performed in HEK293 and COS-7 cells that are not cancer cells (see Figs. 3-6). Thus the relevance of these effects to cancer cannot be predictably extrapolated. Furthermore, the specification has not shown that any changes in the expression of the nucleic acid comprising plexin B1 mutations in any cells affect the phenotype or pathology of any cancer. Additionally, Stratton et al. has not been entered and has not been and will not be considered because Applicants has failed to provide good and sufficient reasons why it was not submitted earlier and thus the evidence therein has not been and will not be considered. Although some of the claimed mutations are found in breast and prostate cancer in vivo, this does not show that the mutations are causative of cancer or that the changes in the expression of these nucleic acids will affect a cancer's growth or development. Thus, the rejection is maintained.

Applicants argue that the Examiner also alleged that the in vitro effects of the claimed mutations described in Wong et al cannot be extrapolated to in vivo anticancer activity.

Applicants argue that however, those skilled in the art routinely infer a putative anti-cancer activity from in vitro testing. Cell lines are routinely used as part of the process for testing new drug. In vivo testing in animals only comes at a late stage in the development process, for reasons of cost and speed. The process of drug discovery demands a target - in this case mutated Plexin B1. A high throughput screen will then be devised to test thousands of agents against either the protein or using a cell-based assay (e.g., www.fluofarma.com). Confirmatory tests will then be undertaken in cell lines with a lead compound. If promising, then a lead compound identified as a putative anti-cancer agent through in vitro assays would be tested in animals.

Applicants argue that this is confirmed by Zips et al (of record), which states on page 3 col 1 Compared to animal tumor models, in vitro methods are less expensive and less time consuming, thereby allowing evaluation of large quantities of new anti-cancer agents. Molecular methods to prove and quantify the potential of several drugs to affect the molecular target...facilitate the selection of promising candidate drugs.

Applicants argue that Zips et al. also states on page 6 col 1; A step-wise procedure from in vitro to in vivo seems reasonable to reduce the large quantity of potential drugs to a few promising agents for further clinical testing.

Applicants argue that the claimed invention is supported by an enabling disclosure.

Applicants' arguments have been considered, but have not been found persuasive. Although in vitro assays with end points known to be relevant to cancer can be used in drug screening assays the claims are defining a new method of screening and neither the specification nor the art of record has established that determining the expression of plexin B1 nucleic acids with mutations at position 5653 or any other of the claimed mutations will indicate a compound is a putative anti-cancer agent. Additionally, applicants appear to be arguing that the method could be used as a screening assay to identify lead compounds with other tests used to confirm the compounds' activity. However, the claims are drawn to identifying a putative anti-cancer agent with the claimed method steps, not screening for a potential anti-cancer agent, thus the method is required to identify the putative anti-cancer agent in the absence of other assays. Thus, for the reasons previously set forth and above the rejection is maintained.

Claims 106, 109 and 111 remain rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement for the reasons set forth in section 5, pages 10-12 of the Office Action of September 25, 2009.

Additionally, the specification remains objected to under 35 U.S.C. 132(a) because the amendment filed Dec. 24, 2008 introduces new matter into the disclosure.

Applicants argue that the Section 112, first paragraph "written description", rejection of claims 106, 109 and 11, and the new matter rejection or objection to the specification stated on pages 12-14 of the Office Action dated September 25, 2009, are obviated by the attached Declaration.

Applicants argue that as discussed with the Examiner during a teleconference on or about November 19, 2009, the cited sections of Rule 57 are not applicable to the present application. The specification refers to the correct accession number. Neither the unamended nor amended claims refer to "the plexinB1 coding sequence of AB0007867.1" as asserted by the Examiner on page 11 of the Office Action dated September 25, 2009. The claims are supported by an adequate written description and the prior amendments to the specification did not introduce new matter. Withdrawal of the Section 112, first paragraph "written description", rejection and the new matter rejection or objection to the specification is requested.

Applicants' arguments have been considered, but have not been found persuasive because the affidavit filed after final has not and will not be entered because Applicants has failed to provide good and sufficient reasons why it was not submitted earlier and thus the evidence therein has not been considered. Thus arguments based on the evidence in the affidavit are moot and claims 106, 109, 111 remains rejected for the reasons previously set forth. Additionally, although the unamended nor amended claims refer to "the plexinB1 coding sequence of AB0007867.1", it is clear as previously set forth that the rejection is based on the claiming of newly added SEQ ID NO: 112. See p. 10, section 5 of the Office action of September 25, 2009.

Additionally, the specification remains objected to for introducing new matter, i.e. SEQ ID NO: 111 and 112 for the reasons previously set forth and above with regard to the section 112 new matter/written description rejection.

